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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/550,173	04/14/2000	Norihisa Ooe	2185-0424-SP	8838

7590 10/03/2002

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EXAMINER
LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/550,173	OOE ET AL.	
	Examiner	Art Unit	
	David Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

Applicant's arguments with respect to claims 1-9 and 11-18 have been considered but are moot in view of the new ground(s) of rejection.

Specification

The disclosure is objected to because of the following informalities: on page 6, the specification refers to claim numbers. The specification cannot refer to claims since the claims can be amended or cancelled during prosecution of the case. Applicant must delete any reference to claim numbers in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no basis found in the specification for the term "inert nucleotide". Applicant has indicated in their amendment dated January 25, 2002 that support for claims 17

and 18 is to be found on page 18 and in Example 15, pages 76-80. These pages have been searched for the term "inert nucleotide", but it has not been found. Therefore, absent evidence to the contrary, this phrase constitutes new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-9, and 11-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 14, 17 and 18 (and all dependent claims) recite the phrase "...said responsive transcriptional control factor..." in step (c). There is insufficient antecedent basis for this limitation in the claim. In the interest of compact prosecution, the limitation is interpreted to mean 'said ligand- responsive transcriptional element'.

Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being vague because it is unclear which reporter gene is being referred to since there are two different reporters recited in the claims from which these depend. In the interest of compact prosecution, it is presumed that Applicant intends for reporter gene (a) to be measured.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. Applicant claims a "...marker gene...which codes a phenotype...", but it is unclear what is meant by this phrase. In the interest of compact prosecution, this phrase is interpreted to mean a 'marker gene...which encodes a polypeptide that confers a phenotype...'.

The term "substantially" in claim 17 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Previously, in Paper 7A filed April 14, 2000, Applicant traversed the use of "substantially" as being indefinite, claiming that the definition with respect to the transcriptional control region. In claim17, the term "substantially" appears to refer to the ability of the transcriptional control region to be changed in terms of an activity, and therefore refers to the activity and not the element itself. Therefore, this rejection is on the use of substantially to describe the activity of the transcriptional control region, and not the transcriptional control region itself. In the absence of a definition of what a substantially unchanged activity would be, the use of the term substantially is indefinite.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. There is no apparent definition of "inert nucleotide" in the specification; therefore the claim fails to point out what is meant by this term. For example, is an inert nucleotide one that renders the transcription control region non-functional or partially functional, or one that has no effect on regulation? It is nearly impossible to interpret the limitation of this claim in the absence of a sufficient definition for "inert nucleotide", but in the interest of compact prosecution.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-9, 11, 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradfield, *et al.* (US Patent No. 5,650,283; henceforth Bradfield), in view of Waldman and Waldman (*Analytical Biochemistry* **258**: 216-222 (1998); henceforth Waldman).

Briefly, Applicant's invention includes (claim1) an animal cell (or kit thereof; claim 13) that stably maintains, on a single DNA molecule, a reporter gene (a) functionally linked to a transcription response element under the control of a ligand-responsive transcription factor (henceforth "LRTF") and a selectable marker (b), but does not contain a reporter gene (c) which is not responsive to said transcription response element. Further limitations (or alternate

versions) of this claim include: the use of a minimum promoter sequence (claim 2; TATA box), the use of different LRTFs (claims 3-8) or a particular LRTF (claim 9; ARNT receptor), the use of a minimum promoter with no sequence that changes the activity of the control region (claim 17) and the insertion of an inert nucleotide into the transcription control region (claim 18). Applicant's invention also describes a method for obtaining said animal cell (claims 14-16), as well as methods of using said cells to screen for agonists and antagonists of said LRTFs.

Bradfield describes the use of mammalian cells expressing the Ah receptor and the ARNT receptor in assays to detect agonists of the transcriptional activities of the receptor (see column 23, lines 30-33 and lines 41-46). The detection assay concerns measuring the activity of a reporter gene that has been operatively linked to a transcriptional response element for the Ah receptor (see column 2, lines 56-62). The Ah receptor is maintained in the cell on a plasmid also containing a selectable marker, while the reporter gene is present on a second plasmid, but in the same molecule with a second selectable marker (see Figure 11). Reporter gene (c) is not present in the cells containing the Ah receptor, reporter and selectable marker genes as described by Bradfield. Applicant previously traversed the teachings of Bradfield, in Paper 7A filed on April 14, 2000, stating that Bradfield did not teach that the DNA was securely maintained in the mammalian cells. Applicant also highlighted that Bradfield fails to teach the use of full length Ah receptor in mammalian cells. In response, the claims of the instant application do not state that the ligand–responsive transcription control factor of the instant invention must be a full-length molecule, thus this argument is considered moot. Regardless, Bradfield explicitly indicates that the Ah receptor and ARNT *or* the chimeric Ah receptor can be expressed in mammalian cells (see column 23, lines 44-46), and not simply the chimeric receptor. This must

be interpreted to mean the full-length Ah receptor was used in the assay described by Bradfield. Therefore, Bradfield teaches all the elements of claims 1, 3-9, 11 and 14-18 except for the secure maintenance of the plasmids in mammalian cells.

Waldman teaches a method for stable transfection of mammalian cells with DNA (see entire document, especially the abstract), where the DNA is securely maintained within the cells for up to 20 generations of growth. Bradfield is modified by Waldman to encompass the stable transfection of mammalian cells with the system described above, thereby teaching all of the elements of claims 1, 3-9, 11 and 13-18. The ordinary skilled artisan would have been motivated to combine these teachings in order to increase the length of time the cells could be assayed, and because the method of Waldman is "fast, economical and of general utility" (see abstract, last sentence). It would have been obvious to combine these methods because a method of transfecting mammalian cells by one manner is applicable to the transfection of any mammalian cell, and both Waldman and Bradfield refer to methods of transfecting mammalian cells. Furthermore, Applicant has merely extended the length of time in which the cells maintain the plasmids of interest with respect to Bradfield, which any method of stable transfection would suffice to do. Therefore, this step does not render the instant invention novel with respect to Bradfield.

Given the teachings of the stated prior art and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 2 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradfield, in view of Waldman and in further view Kushner, *et al.* (US Patent No. 6,117,638; henceforth Kushner).

Applicant's invention is as described above.

Bradfield in view of Waldman teaches the invention as described above, but does not teach the following elements: The use of a TATA box in the minimum promoter element (claim 2), or the identification of an antagonist for the LTRF (claim 12).

Kushner teaches a method for screening compounds in cells (including mammalian) that both activate (agonist) and block (antagonist) the stimulation of transcription of genes, some of which are regulated by hormone receptors, using a minimal promoter region comprised of a TATA box (see especially column 14, lines 39-49 and 57-64 and column 15, lines 32-41 and 60-63). Bradfield in view of Waldman is modified by Kushner to encompass the limitations of screening for antagonists in the assay of Bradfield and using a minimum promoter comprising a TATA box to accomplish this task. The ordinary skilled artisan would have been motivated to combine these teachings to identify compounds which could attenuate (antagonize) the affects of hormone receptor transcription response hyperactivation, which is prevalent with respect to the estrogen receptor and its role in breast cancer formation (see Kushner column15, line 40-41), and also to determine the effects of the compound in the absence of other transcription elements which could possibly adversely affect the detection of the reporter gene. It would have been obvious to combine these teachings because the methods of Bradfield in view of Waldman and Kushner are both related to the identification of compounds that affect transcription; therefore the methods are sufficiently related to merit combination.

Given the teachings of the stated prior art and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
September 24, 2002

DAVID GUZO
PRIMARY EXAMINER

WEST Search History

DATE: Monday, August 26, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ			
L7	L6 same selecti$	8	L7
L6	estrogen receptor same reporter	127	L6
L5	l2 same selective	5	L5
L4	l2 same neomycin	6	L4
L3	L2 same eukaryotic	13	L3
L2	L1 same reporter	349	L2
L1	inducibl$ near2 promoter$	8575	L1

Attachment to paper #15 2nd Action After RCE

END OF SEARCH HISTORY

WEST Search History

DATE: Monday, August 26, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ			
L5	L4 same selectiv$	1	L5
L4	hormone near5 reporter	204	L4
L3	L2 same eukaryotic	3	L3
L2	L1 same selecti$	87	L2
L1	hormone same reporter	873	L1

END OF SEARCH HISTORY

WEST Search History

DATE: Tuesday, August 27, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,EPAB,DWPI; PLUR=YES; OP=OR			
L9	l7 near10 (COS or hela or HepG2 NIH3t3 or mouse)	25	L9
L8	L7 near5 (mammalian adj3 cell$1)	0	L8
L7	L6 near5 reporter	193	L7
L6	L5 or (inducible near5 response adj element$1)	17087	L6
L5	(inducible near5 promoter$2) or (gre or ppre or ere or are or tre or dre or xre)	17081	L5
L4	l2 near10 eukaryotic	0	L4
L3	L2 near10 eukary$5	0	L3
L2	L1 near10 reporter	265	L2
L1	(inducible near5 promoter$2) or (gre orppre or ere orare or tre or dre or xre)	14155	L1

END OF SEARCH HISTORY